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Serum copeptin as severity and prognostic marker in hyperglycemic emergencies

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ABSTRACT

Despite the high mortality and morbidity associated with hyperglycemic emergencies (HEs), reliable biological markers that could predict the severity and prognosis are largely unavailable. This study therefore, assessed the performance of copeptin in predicting the severity and prognosis of HEs. Sixty patients with HEs [27 with diabetes ketoacidosis (DKA) and 33 with hyperglycemic hyperosmolar state (HHS)] were recruited into this cross-sectional study. Serum copeptin was determined using ELISA. Glasgow Coma Scale (GCS) was used to grade the severity of HE and the performance of copeptin in predicting the severity of HE was determined using the Area under the Receiver Operating Characteristic Curve (AUROC). Data analysis was done using the Student's t-test, Mann Whitney U and Spearman correlation as appropriate. $P<0.05$ was considered as statistically significant. The median copeptin level was slightly higher in patients with HHS than in patients with DKA. In patients with moderately severe score of GCS (GMo), the median copeptin level was significantly higher when compared with patients with normal GCS score (GN). Assessing the performance of copeptin in predicting the severity of HE, copeptin had AUROC of 6.334 ($P = 0.034$) for GN and 0.738 ($P = 0.011$) for GMo. During the study, 10 patients (16.7%) died but the median copeptin level was only slightly higher in the patients that died (PD) than in patients that survived (PS). Also, the median copeptin level in patients who survived and were on admission for ≥ 11 days was slightly higher than in those that were admitted for ≤ 10 days. There was a significant inverse correlation between copeptin and GCS scores. Copeptin might not be a good prognostic marker in patients with hyperglycemic emergencies but had good performance in predicting patients with hyperglycemic emergencies with normal and moderately severe GCS scores

Keywords: Copeptin, Glasgow coma scale, Hyperglycemic emergencies, Osmolarity, Prognosis

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INTRODUCTION

Hyperglycemic emergencies (HEs) are life-threatening endocrine metabolic emergencies with significant morbidity and mortality [1]. Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) constitute the hyperglycemic emergencies and remain the most serious acute metabolic complications of diabetes mellitus [2].

A National Diabetes Data Group in America reported that the incidence of DKA vary between 4.6 and 8.0 per 1000 person-years, while that of HHS is less than 1 per 1000 person-years among patients with diabetes [3]. In Nigeria, Ogbera *et al*. [4] reported that cases of DKA are commoner than HHS in Nigerian diabetics.

Although DKA and HHS are distinct entities as they differ by the severity of dehydration and presence of ketosis and metabolic acidosis, patients can still present with elements of both conditions in up to 30% of cases [5 – 7].

Despite the high mortality and morbidity associated with HEs, reliable biological markers that could help in rapid diagnosis, severity grading and prognosis which are vital in reducing morbidity and mortality are largely unavailable.

One of the widely studied biomarkers with proven information on diagnostic performance, severity stratification and prognosis in a number of diseases is copeptin. Copeptin, a 39 amino acid peptide, is co-secreted (in equimolar ratio) with arginine vasopressin (AVP) from the neurohypophysis upon hemodynamic or osmotic stimuli. It is more stable and has longer half-life than AVP and can easily be measured as AVP surrogate [8, 9].

Serum copeptin level has been shown to be a predictor of survival in lower respiratory tract infection, leptospirosis, bacteria sepsis, cardiovascular disease, stroke, acute exacerbations of chronic obstructive pulmonary disease, hemorrhagic and septic shock, traumatic brain injury and in critically ill patients [10 – 15]. It has also been shown to be an independent predictor of mortality and morbidity in patients with heart failure [16 – 18]. Recently, Asferg *et al*. [19] showed that elevated copeptin is associated with abnormalities in glucose and insulin metabolism. Similarly, Saleem *et al*. [20] and Enhörning *et al*. [21] reported that copeptin is a predictor of increased risk for diabetes mellitus and is a marker for insulin resistance.

Presently, there is no available report on the ability of copeptin to predict the severity and prognosis of HEs. Identification of reliable biomarkers that could assist Physicians in prediction of severity and possible outcome in individuals presenting with hyperglycemic emergencies is therefore of clinical importance. This could facilitate quick intervention and quality management of the patients.

MATERIALS AND METHODS

Subjects

A total of 60 consecutive patients (aged 19 - 75years) were recruited into this longitudinal cross sectional study. They comprised 27 individuals with DKA and 33 with HHS that presented to the Accident and Emergency Department and the Endocrinology Unit, Medical Outpatient (MOP) of the University College Hospital, Ibadan, Nigeria.

Ethical consideration

All the participants were enrolled after an approval from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee (UI/EC/13/0089). Written informed consent was also obtained from each participant or otherwise, assents from their appropriate relative.

Diagnosis of DKA and HHS

DKA was diagnosed as a blood glucose of >250 mg/dL, moderate ketonuria or ketonemia, and a bicarbonate of <15 mEq/L while HHS was diagnosed as a severely elevated glucose (>600 mg/dL), minimal or no ketonuria or ketonemia, a bicarbonate of >15 mEq/L and sensorium alteration (Kitabchi *et al*., 2009).

Exclusion criteria

Subjects that just recovered from acute myocardial infarction or with established thyroid and adrenal endocrinopathies and those on corticosteroids were all excluded from the study. Also, patients with heart failure, end stage renal disease, and pregnancy were excluded.

Data collection and blood pressure measurement

A short structured questionnaire was used to obtain information on demography, alcohol use, drug use, medications and established diseases. Blood pressure (BP), heart rate and respiratory rate (RR) were determined using standard methods while mean arterial BP (MAP) was calculated as the addition of 2/3 of diastolic BP and 1/3 of systolic BP.

Blood sample collection

About 10 ml of venous blood was collected from each participant upon presentation and dispensed into lithium heparin, fluoride oxalate and plain bottles as appropriate. Plasma and serum samples obtained were stored at -20^{0}C

until analyzed.

Assay methodology
Serum copeptin level was measured using ELISA (Glory Biosciences, USA). Plasma glucose was determined using glucose oxidase method while plasma sodium (Na^+), potassium (K^+), chloride (Cl^-) and HCO_3^- were determined using ion selective electrode (ISE 4000SFRI). Serum creatinine and urea were determined using Jaffe and enzymatic methods respectively. The Coulter Hematology Analyzer (Sysmex xT.1000i) was used for the determination of the total white blood cell count (TWBC) and hematocrit. Thereafter, osmolarity was calculated as 2[Na (mmol/l)] + 2[K (mmol/l)] + [Urea (mmol/l)] + [glucose (mmol/l)].

Determination of HE severity and classification
Glasgow Coma Scale (GCS) was used to grade the severity of HE. GCS is a measure of the response of patient putting into cognizance the motor, verbal and eye response. Scores of 0-5, 6-10, 11-14 and 15 were graded as severe, moderate, mild and normal respectively [22].

Statistical analysis
The distribution of the variables was assessed using histogram with normal curve. Thereafter, variables with Gaussian distribution were compared using the Student's t-test while Mann-Whitney *U* was used to compare variables that were not normally distributed. The association between variables was assessed using Spearman correlation. Area under the Receiver Operating Characteristic Curve (AUROC) was used to determine if serum copeptin level could differentiate between the various severity groups obtained from the GCS scores. *P*-values less than 0.05 were considered to be statistically significant.

RESULTS

Table 1 shows the characteristics of the study participants.

In Table 2, participants with HHS were compared with DKA. It was observed that only the mean age and SBP were significantly lower in DKA compared with HHS. Although the mean glucose and median copeptin levels were higher in participants with HHS compared with DKA, the difference did not reach level of statistical significance.

All the participants were pulled together and the level of HE severity was determined using GCS. Using the scores obtained, the study participants were classified as normal (GN), mild (GM), moderate (GMo) and severe (GS). The median copeptin level in GMo was significantly higher when compared with GN. Also, the mean K^+ and HCO_3^- were significantly lower in GMo compared with GM. The mean glucose level was significantly lower in GS compared with GN and in GS compared with GM. Similarly, the mean levels of glucose and DBP were significantly lower in GS compared with GMo (Table 3).

Although the median copeptin level was only significantly higher in GMo compared with GN, we sought to know if serum copeptin level could be a useful tool in stratifying patients with HE into different severity groups based on GCS scores. It was observed that the area under the curve (AUROC) was significant in patients with normal and moderate GCS scores (Table 4, Figure 1).

During the study, 10 participants (16.7%) died. The clinical and biochemical parameters were compared between the participants that died) and the 50 (83.3%) participants that survived. It was observed that death occurred in those who died within the first few days of hospital admission as the median length of hospital stay was significantly lower compared with those who survived. Also, the mean TWBC level was significantly higher in patients that died compared with those who survived. However, the elevated median level of copeptin in patients that died compared with those who survived was not statistically significant (Table 5).

Using length of hospital stay as an index of prognosis, the patients who survived were further classified into 2 groups: those that were on admission for ≤ 10 days and those admitted for ≥ 11 days. It was observed that majority (64%) of patients who survived were on admission for more than 10 days. The mean age of patients who were on admission for ≥ 11 days was significantly higher compared with those that stayed for ≤ 10 days. However, copeptin and TWBC were insignificantly elevated in patients who were on admission for ≥ 11 days compared with those that stayed for ≤ 10 days (Table 6).

As shown in Table 7, copeptin had significant positive correlation with SBP and urea but had a significant negative correlation with GCS scores.

Table 1: Characteristics of the study participants

Parameters	HE patients (n = 60)
Systolic BP (mmHg)	131.77 ± 36.75
Diastolic BP (mmHg)	77.37± 26.69
Mean arterial BP (mmHg)	94.41 ± 27.48
Heart rate (bpm)	103.88± 17.04
RR (b/min)	29.08 ± 10.59
TWBC (10^6/µL)	11.10 (7.71 – 13.68)
PCV (%)	32.08 ± 9.12
Glucose (mg/dl)	520.00 ± 91.42
Na^+ (mmol/l)	139.43 ± 7.67
K^+ (mmol/l)	3.94 ± 1.20
HCO^-_3 (mmol/l)	16.78 ± 6.13
Urea (mg/dl)	50.00 (23.50 -81.50)
Creatinine (mg/dl)	1.50 (0.83-2.55)
Osmolarity (mosmol/l)	323.93 ± 21.74
Copeptin (pg/ml)	1.30 (1.13-2.20)
GCS	11.08 ± 4.40

Results are in mean ±standard deviation or median (interquartile range), bpm=beats per minute, b/min=breaths per minute

Table 2: Clinical and biochemical parameters in patients with HHS and DKA

Parameters	HHS (n = 33)	DKA (n = 27)	*P*-value
Age (years)	54.52 ± 15.50	45.44 ± 15.55	0.028*
Systolic BP (mmHg)	141.18 ± 39.31	120.26 ± 30.20	0.027*
Diastolic BP (mmHg)	82.82 ± 29.53	70.70 ± 21.45	0.080
Mean arterial BP (mmHg)	99.03 ± 29.13	88.76 ± 24.68	0.152
Heart rate (bpm)	101.61 ± 17.49	106.67 ± 16.36	0.256
RR (b/min)	28.24 ± 11.77	30.11 ± 9.05	0.501
TWBC (10^6/µL)	13.37 ± 8.51	11.81 ± 5.71	0.419
PCV (%)	32.44 ± 7.94	31.63 ± 10.53	0.735
Glucose (mg/dl)	531.00 ± 84.53	508.59 ± 99.42	0.349
Na^+ (mmol/l)	139.76 ± 8.00	139.04 ± 7.37	0.720
K^+ (mmol/l)	3.88 ± 1.22	4.00 ± 1.20	0.708
HCO^-_3 (mmol/l)	18.12 ± 6.35	15.15 ± 5.55	0.061
Urea (mg/dl)	48.00 (23.00 – 80.00)	55.00 (24.00 – 82.00)	0.485
Creatinine (mg/dl)	1.50 (0.80 – 2.40)	1.60 (0.90 – 2.70)	0.552
Osmolarity (mosmol/l)	324.64 ± 17.05	323.07 ± 26.72	0.785
Copeptin (pg/ml)	1.50 (1.15 – 2.50)	1.20 (1.10 – 2.20)	0.468
GCS	11.24 ± 4.25	10.89 ± 4.65	0.760

*Results are in mean ±standard deviation or median (interquartile range), *significant at P<0.05, bpm=beats per minute, b/min=breaths per minute*

Table 3: Demographic, clinical and biochemical parameters based on GCS score

	Normal (n = 22)	Mild (n = 17)	Moderate (n = 13)	Severe (n = 8)
Systolic BP (mmHg)	129.77 ± 32.52	127.00 ± 28.65	150.58 ± 42.12	121.73 ± 45.44
Diastolic BP (mmHg)	77.27 ± 23.40	76.87 ± 21.19	89.17 ± 34.59	65.36 ± 27.97[c]
MAP (mmHg)	92.24 ± 26.41	94.91 ± 21.61	104.9 ± 31.61	86.58 ± 32.00
Heart rate (bpm)	101.95 ± 18.69	101.67 ± 16.37	105.58 ± 20.06	108.91 ± 10.67
RR (b/min)	27.77 ± 6.79	29.53 ± 9.56	26.17 ± 6.789	34.27 ± 18.59
PCV (%)	32.27 ± 8.38	30.93 ± 9.98	33.37 ± 10.67	31.81± 8.62
Glucose (mg/dl)	499.05 ± 95.83	529.04 ± 79.48	526.66 ± 94.83	487.00 ± 79.48[a,b,c]
Na^+ (mmol/l)	138.55 ± 6.52	139.40 ± 7.25	140.00 ± 9.86	140.64 ± 8.55
K^+ (mmol/l)	3.66± 0.02	4.46± 0.96	3.39 ± 0.84[b]	4.15 ± 0.94
HCO^-_3 (mmol/l)	17.27 ± 4.75	18.60 ± 8.72	13.67 ± 4.20[b]	16.73 ± 5.83
Urea (mg/dl)	47.5 (21.50 - 76.25)	62.00 (27.00 - 105.0)	33.00 (20.75 - 92.50)	53.00 (45.00 - 70.00)
Creatinine (mg/dl)	1.50 (0.78 - 2.02)	1.90 (0.80 - 4.50)	1.60 (0.83 - 2.53)	1.90 (0.90 - 2.60)
Osmolarity (mosmol/l)	319.09 ± 15.46	325.47 ± 13.394	326.58 ± 24.64	328.64 ± 35.78
Copeptin (pg/ml)	1.20 (1.00 - 1.50)	1.30 (1.00 - 2.20)	2.10 (1.38 - 4.23)[a]	1.50 (1.20 - 2.20)

Results are in mean ±standard deviation or median (interquartile range), normal=GCS score 15, mild=GCS score 11 – 14, moderate=GCS score 6 – 10, severe=GCS score 0- 5, [a]significantly different from normal, [b]significantly different from mild, [c]significantly different from moderate, bpm=beats per minute, b/min=breaths per minute

Table 4: Area under the curve for copeptin in patients with hyperglycemic emergencies based on GCS scores

			95% Confidence Interval	
	Area	*P*-value	Lower boundary	Upper boundary
Normal	0.634	0.034*	0.280	0.624
Mild	0.452	0.579	0.280	0.624
Moderate	0.738	0.011*	0.593	0.882
severe	0.563	0.516	0.393	0.733

**Significant at P<0.05*

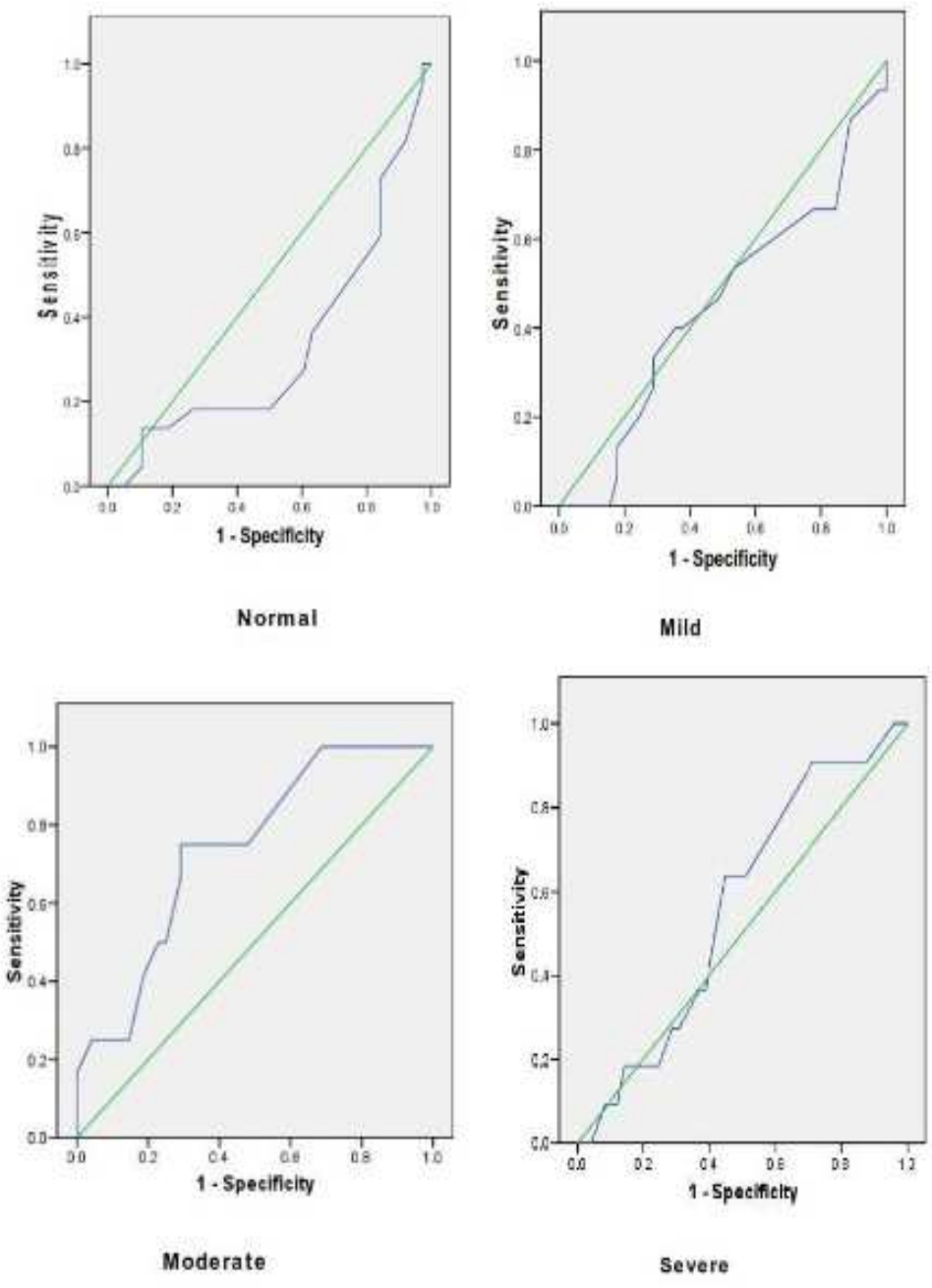

Figure 1: ROC curves for copeptin based on GCS scores

Table 5: Demographic, clinical and biochemical parameters in patients that survived (PS) and those that died (PD)

Variables	PS (n = 50)	PD (n = 10)	*P*-value
Age (years)	50.12 ± 16.85	52.00 ± 11.83	0.677
Length of stay (days)	14.00 (7.00 - 15.25)	4.00 (2.00 - 7.25)	0.005*
Systolic BP (mmHg)	132.46 ± 39.88	128.30 ± 13.98	0.557
Diastolic BP (mmHg)	78.70 ± 27.98	70.70 ± 18.69	0.275
MAP (mmHg)	96.84 ± 27.27	82.26 ± 26.52	0.138
RR (b/min)	29.12 ± 11.02	28.90 ± 8.57	0.945
Heart rate (bpm)	103.32 ± 17.42	106.70 ± 15.52	0.548
PCV (%)	33.05 ± 9.18	27.20 ± 7.41	0.450
TWBC (10^6/µL)	11.73 ± 6.10	17.381 ± 11.10	0.025*
Glucose (mg/dl)	523.84 ± 89.70	506.30 ± 103.41	0.626
Na^+ (mmol/l)	139.40 ± 7.66	139.40 ± 8.14	0.988
K^+ (mmol/l)	139.40 ± 7.65	139.40 ± 8.14	0.989
HCO^-_3 (mmol/l)	16.14 ± 5.56	20.00 ± 8.03	0.175
Urea (mg/dl)	48.50 (23.00 - 75.00)	75.45 (43.00 - 114.50)	0.084
Creatinine (mg/dl)	1.50 (0.80 - 2.45)	1.90 (1.28 - 2.95)	0.518
Osmolarity (mmol/l)	323.00 ± 22.04	328.60 ± 0.52	0.452
Copeptin (pg/ml)	1.30 (1.18 - 2.50)	1.40 (1.00 - 2.13)	0.780

*Results are in mean ± standard deviation or median (interquartile range), MAP = mean arterial pressure, RR = Respiratory rate, PCV = packed cell volume, TWBC = Total white blood count. *Significant at P<0.05, bpm=beats per minute, b/min=breaths per minute*

Table 6: Differences in demographic, clinical and biomedical parameters in patients with hyperglycemic emergencies based on length of hospital stay with the exemption of the subjects that died

Variables	≤10 days (n = 18)	≥11 days (n = 32)	*P*-Value
Mean (days)	5.39 ± 2.38	18.34 ± 9.57	0.000*
Age (years)	43.72 ± 16.99	53.72 ± 15.92	0.043*
Systolic BP (mmHg)	122.94 ± 35.35	137.81 ± 41.79	0.209
Diastolic BP (mmHg)	70.17 ± 21.08	83.50 ± 30.45	0.106
MAP (mmHg)	90.37 ± 17.57	100.48 ± 31.11	0.212
RR (b/min)	25.56 ± 5.38	31.13 ± 12.83	0.086
Heart rate (bpm)	101.61 ± 19.94	104.28 ±16.09	0.608
TWBC (10^6/L)	10.50 (7.36 - 12.75)	11.00 (7.74 - 13.00)	0.606
PCV (%)	31.00 ± 9.89	34.20 ± 8.76	0.240
Glucose (mg/dl)	519.38 ± 87.00	526 ± 98.43	0.795
Na^+ (mmol/l)	138.22 ± 8.67	140.13 ± 7.07	0.404
K^+ (mmol/L)	3.60 ± 0.98	3.90 ± 1.19	0.473
Creatinine (mg/dl)	1.70 (0.87 - 2.35)	1.50 (0.80 - 2.90)	0.911
Urea (mg/dl)	47.00 (19.70 - 66.75)	49.00 (24.50 - 81.50)	0.390
HCO^-_3 (mmol/l)	16.00 ± 3.99	16.22 ± 6.33	0.895
Osmolarity (mosmol/l)	322.00 ± 23.43	323.56 ± 21.59	0.813
Copeptin (pg/ml)	1.20 (1.18 - 2.60)	1.50 (1.05 - 2.43)	0.744

**Significant at P<0.05, results are in mean ± standard deviation or median (interquartile range), bpm=beats per minute, b/min=breaths per minute*

Table 7: Spearman's correlation between copeptin and systolic blood pressure, urea and GCS scores in participants with hyperglycemic emergencies

	COPEPTIN	
	r-value	*P*-value
Systolic BP (mmHg)	0.342	0.007*
Urea (mg/dl)	0.288	0.026*
GCS	-0.284	0.028*

**Significant at P<0.05*

DISCUSSION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most common and most serious diabetic emergencies [23]. In this study, participants with HHS were older than those with DKA. Usually, HHS affects older patients with type 2 diabetes mellitus (T2DM), although it is reported in all age groups [2, 24, 25].

Reports have shown that there is frequent coexistence between hyperglycemia and hypertension and that hyperglycemia play a role in hypertension development [26, 27]. This probably explains our observed elevated systolic blood pressure in HHS compared with DKA as the participants with HHS had elevated glucose level.

Acute illnesses such as hyperglycemic emergencies have been shown to activate hypothalamo-pituitary-adrenal (HPA) axis leading to increased production of its various hormones. Our observed elevated level of copeptin in GMo compared with GN is in line with the report of Katan and Christ-Crain [28] which showed that copeptin has the ability to mirror individual stress level and disease severity.

Serum bicarbonate level has been shown to decrease with severity of DKA [6, 29]. Similarly, it has been reported that patients with hyperglycemic crises could present with low-normal or low potassium concentration which usually require careful cardiac monitoring and vigorous K^+ replacement. Careful monitoring is usually required as treatment can lower potassium further thus, provoking cardiac dysrhythmia [6]. Our observed lower levels of K^+ and HCO_3^- in GMo compared with GM probably indicates that patients with moderately severe HE have K^+ and HCO_3^- depletion than GM and hence, may require quick intervention to restore electrolyte balance.

Although blood samples were collected upon admission in the study participants, we observed lower level of DBP in GS compared with GMo and lower level of glucose in GS compared with GN and in GS compared with GMo. Also, when the performance of copeptin for HE severity stratification was assessed, copeptin had good performance in identifying HE patients with normal and moderately severe GCS scores. This observation supports our earlier observed significant elevation of copeptin level in GMo compared with GN. There was progressive rise in the median levels of copeptin from GN through GMo only to reduce in GS. These observations are unexpected and cannot be presently explained. Perhaps, pulling patients with DKA AND HHS together could be a significant confounder responsible for the observation. Also, since GCS only considers the motor, verbal and eye response of a patient, biochemical changes such as osmolality might not be well captured by the scale. It is known that sensorium in HHS is usually related to osmolality whereas in DKA, it is related to acidosis.

Worldwide, infection is the most common precipitating cause of DKA and HHS [30 – 32]. Similarly, mild leucocytosis (due to stress, dehydration and demargination of leucocytes without any underlying infections) has been reported as a common observation in patients with DKA [23]. Our observed elevated TWBC in participants that died (PD) compared with participants that survived (PS) could therefore be due to either infection, stress, dehydration, demargination of leucocytes or a combination of all.

The mortality from HEs still remains high despite improved care [23]. The death of 10 patients (16.7%) within a median of 4 days probably indicates that early detection and timely intervention are important factors in reducing the mortality from HEs.

The median copeptin level was not significantly elevated in participants who stayed for ≥11 days compared with those who stayed for ≤10 days. Although no report is available on the prognostic properties of copeptin in HEs, our observation is similar to that of Akinlade et al. [33] which showed that copeptin is not a good marker to determine the outcome of vaso-occlusive crisis in individuals with sickle cell anemia. Insignificant elevation in the median copeptin levels in participants that died (PD) and in those that stayed for ≥11 days indicate that copeptin might not be a good prognostic marker for HEs using death and length of hospital stay as outcomes. However, participants that were admitted for ≥11 days were older than those who were admitted for ≤10 days. This probably suggests that older patients with HEs do not recover as promptly as the younger ones.

Appropriate activation of the hypothalamic-pituitary-adrenal (HPA) axis is essential for survival during critical illness [34, 35]. The observed inverse correlation between copeptin and scores obtained from GCS indicates that there is concomitant rise in copeptin level as severity of HE increases (as demonstrated by low GCS score). This further confirms our earlier observation that the GMo group had significantly elevated copeptin level compared with the GN group. Also, the observed positive correlation between copeptin and SBP as well as copeptin and urea indicates that the higher the levels of SBP and urea, the higher the activation of the HPA axis and the higher the production of copeptin.

It could therefore be concluded from this study that copeptin might not be a good prognostic marker in patients with hyperglycemic emergencies but had good performance in predicting patients with hyperglycemic emergencies with normal and moderately severe GCS scores.

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